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EXAMINER	
YAEN, CHRISTOPHER H	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,280	OHTA ET AL.	
	Examiner	Art Unit	
	CHRISTOPHER H. YAEN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *9-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☒ Claim(s) *1-3,5,6 and 8* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/23/05, 8/21/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election of group 2 (claims 1-8, drawn in part to a fusion gene comprising a gene encoding an NGR homing peptide, a gene encoding a GFP, and a gene encoding delta NBax) in the reply filed on 2/5/2008 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election **without traverse** (MPEP § 818.03(a)).

2. Claims 1-15 are pending, claims 9-15 are withdrawn from further consideration as being drawn to non elected subject matter. Applicant is reminded to cancel claims drawn to non-elected inventions.

3. Claims 1-8 are examined on the merits. It is noted that claims 1-8 are examined only to the extent that the claims read on the a fusion gene comprising a gene encoding an NGR homing peptide, a gene encoding a GFP, and a gene encoding ΔNBax.

Information Disclosure Statement

4. The Information Disclosure Statements filed on 9/23/2005 and 8/21/2006 are acknowledged and considered. Signed copies of the IDS are attached hereto.

Claim Objections

5. Claims 1,2,3,5,6, and 8 are objected to because of the following informalities:

a. Claims 1,2,3, and 5 are objected because they recite subject matter drawn to non-elected inventions.

b. Claims 6 and 8 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claims 4 and 5. See MPEP § 608.01(n). Accordingly, the claims 6 and 8 are not been further treated on the merits.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd paragraph

6. Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims 1 and 4 are rejected as vague and indefinite for reciting the term "ΔNBax" as the sole means of identifying the claimed molecule. The use of laboratory designations only to identify a particular molecule renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct molecules. The rejection can be obviated by amending the claims to specifically and uniquely identify ΔNBax, for example, by SEQ ID NO. and function of ΔNBax.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a **publication** is improper. Applicant is required to

amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

An application as filed must be complete in itself in order to comply with 35 U.S.C. 112; however this does not bar incorporation by reference. Ex parte Schwarze, 151 USPQ 426 (Bd. of Appeals, 1966). an application for a patent when filed may incorporate "essential material" by reference to (1) a United States patent or (2) an allowed U.S. application, subject to the conditions set forth below. "Essential material" is defined as that which is necessary to (1) support the claims, or (2) for adequate disclosure of the invention (35 U.S.C. 112). "Essential material" may not be incorporated by reference to (1) patents or applications published by foreign countries or regional patent offices, to (2) non-patent publications, to (3) a U.S. patent or application which itself incorporates "essential material" by reference or to (4) a foreign application. See In re Fouche, 169 USPQ 429; 439 F.2d 1237 (CCPA 1971).

Nonessential subject matter may be incorporated by reference to (1) patents or application published by the United States or foreign countries or regional patent offices, (2) prior filed, commonly owned U.S. applications or (3) non-patent publications, for purposes of indicating the background of the invention or illustrating the state of the art.

The referencing application must include (1) an abstract, (2) a brief summary of the invention, (3) an identification of the referenced patent or application, (4) at least one view in the drawing in those applications admitting of a drawing, and (5) one or more claims. Particular attention should be directed to specific portions of the referenced patent or application.

In this case, the invention has relied on the sequence information pertaining to the *bax* gene by reference to a reference a non patent literature, Biochem. Biophys. Res. Commun. 1998 Feb 13; 243 (2):609-616. Such incorporation is improper as set forth above and the applicant is required to amend the specification to include the sequence information provided in the cited reference.

Applicant is reminded to provide said Sequence Listing which complies with the requirements of 37 CFR 1.821 through 1.825 for Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant is reminded to provide the appropriate Hawkins Declaration to accompany amending the instant specification.

Claim Rejections - 35 USC § 112, 1st paragraph

8. Claims 1-4 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A WRITTEN DESCRIPTION REJECTION.

The specification teaches a gene encoding a ΔNBax protein comprising amino acids 112-192 of the bax protein as defined by reference to Biochem Biophys Res Commun. 1998 Feb 13; 243 (2):609-616 (see pg 1 of the specification) and missing the NH2 domain deleted from Bax. However, the specification fails to disclose the breadth of the ΔNBax proteins the claims currently encompass. Specifically, the claims encompass sequence which are not taught in the specification, such as ΔNBax proteins derived from other species as well as ΔNBax proteins which are either shorter or longer than that described in the specification (see for example pg 1). Thus the written description in this case has only described a ΔNBax proteins as defined in the specification on page 1 and therefore not commensurate in scope to any ΔNBax proteins as currently claimed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a recitation of the term " ΔNBax ". Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Although drawn to DNA arts, the findings in *University of California v. Eli Lilly and*

Co., 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997) and *Enzo Biochem, Inc. v. Gen-Probe Inc.* are relevant to the instant claims. The Federal Circuit addressed the application of the written description requirement to DNA-related inventions in *University Of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). The Court stated that" [a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name', of the claimed subject matter sufficient to distinguish it from other materials. " Id. at 1567, 43 USPQ2d at 1405. The court also stated that:

> a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA" without more, is not an adequate written description of the genus because it does not distinguish the genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406. The court concluded that "naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material." Id.

Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling

within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id.

The Federal Circuit has recently clarified that a DNA molecule can be adequately described without disclosing its complete structure. See *Enzo Biochem, Inc. V. Gen-Probe Inc.*, 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The *Enzo* court adopted the standard that "the written description requirement can be met by show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics .... i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Id.* at 1324, 63 USPQ2d at 1613 (emphasis omitted, bracketed material in original).

Thus the instant specification may provide an adequate written description of ΔNBax, per *Lilly*, by structurally describing representative ΔNBax proteins or by describing “structural features common to the members of the genus, which features constitute a substantial portion of the genus." Alternatively, per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics."

It is also noted that the written description in this case has not set forth an adequate written description of sequence encompassed by the sequence which are

"complementary" to a DNA hybridizing to a sequence of DNA as set forth in SEQ ID No: 3. The rationale underlying this rejection is essentially the same as set forth above as it applies to the recitation of the term ΔNBax. It is noted that applicant may overcome this portion of the written description rejection by amending the claim to recite "a full complement" or "completely complementary to".

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was

not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-4 and 6-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Aokage *et al* (Biochem Biophys Res Commun. 2004; 341(3):711-716; IDS 2005 AJ) and Ellerby *et al* (Nature Medicine 1999; 5(9):1032-1038) or US Patent 6,576,239 (Ruoslahti *et al*) in view of Ishibashi et al (Biochem Biophys Res Commun. 1998 Feb 13; 243 (2):609-616) of Usui *et al* (Oncogene 2003; 22:2655-2663; IDS 2006 AQ).

a. Aokage *et al* teach a gene comprising GFP fused to the Bax gene (see Material and Methods section). Aokage *et al* however fail to disclose a GFP-ΔNBax fusion construct. However this deficiency is remedied by Ishibasi *et al*.

b. Ishibashi *et al* teach the construction of the ΔNBax construct.

c. Ellerby *et al* or US Patent 6,576,239 teach the construction of a NGR tumor homing fusion protein where the protein is able to target to tumor endothelial areas or angiogenic areas (see US Patent 6,576,239 for example).

It would have been prima facie obvious to those of ordinary skill in the art to combine the different components taught in the art to form the instantly claimed invention. It is prima facie obvious to combine known elements in the art to form a new product. In this case, it would have been obvious because Aokage et al taught the construction of a GFP-Bax fusion gene product, those of skill in the art could have substituted the Bax gene with an ΔNBax gene as taught by Ishibashi *et al* because ΔNBax was known to those in the art as having cell death activity which was not inhibitable by a pan-caspase

inhibitor (see Usui *et al*). Moreover, it was known in the art at the time of the invention that NGR was a homing peptide capable of locating to angiogenic areas (see either Ellerby *et al* or Rouslathi *et al*). It would have been routine in the art at the time of the invention to substitute the KLAKLAR sequence with that of the GFP- ΔNBax gene such to make the instantly claimed invention. Such a substitution is routine and within the level of skill in the art at the time of the invention.

Thus a method production as instantly claimed would also be obvious in view of the references cited above.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CHRISTOPHER H. YAEN whose telephone number is (571)272-0838. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic

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/Christopher H Yaen/
Primary Examiner, Art Unit 1643